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# Oxazolinethiones and Oxazolidinethiones for the First Copper-Catalyzed Desulfurative Cross-Coupling Reaction and First Sonogashira Applications

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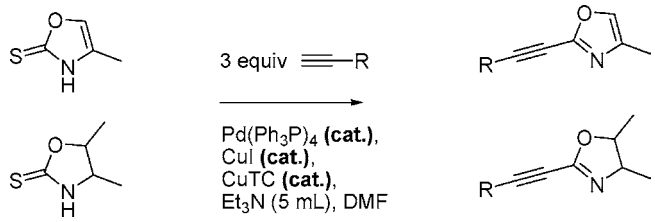
## ABSTRACT




**Cyclic thionocarbamates, namely chiral oxazolidinethiones (OZT) and aromatic oxazolinethiones (OXT), were involved, for the first time, in Sonogashira cross-coupling. A cooperative effect of two different copper (I) species—CuI and CuTC—accounts for this new copper-catalyzed desulfurative carbon–carbon cross-coupling reaction. This cooperative reactivity could also be extended to other copper (I) catalysts.**

Despite the tremendous methodological variety of transition metal-catalyzed cross-coupling protocols known today,[1] there is still room for alternative methods that would overcome the stability problems of sensitive electrophiles and significantly extend the versatility of the processes. In recent years, heteroaromatic thioethers have been introduced as a new class of electrophiles for their greater stability.[2] The alkylsulfanyl method developed by Liebeskind and Srogl, mostly onto heteroaromatic templates,[3] can be regarded as a reliable

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(1) For reviews, see : (a) Heck, R. F. *Palladium Reagents in Organic Synthesis;* Academic Press: New York, 1985. (b) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley & Sons: New York, 1995. (c) Stille, J. K. *Angew. Chem., Int. Ed.* **1986**, *25*, 508−524. (d) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (e) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211. (f) Dubbaka, S. R.; Vogel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 7674−7684. (g) Metal-Catalyzed Cross-Coupling Reactions, 2nd ed.; de Meijere, A.; Diederich, F.; Eds.; Wiley-VCH: Weinheim, Germany, **2004**; Vols.1 and 2.

(2) (a) Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260−11261. (b)Yu, Y.; Liebeskind, L. S. *J. Org. Chem.* **2004**, *69*, 3554−3557. (c) Yang, H.; Li, H.; Wittenberg, R.; Egi, M.; Huang, W.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007**, *129*, 1132−1140. (d) Leconte, N.; Keromnes-Wuillaume, A.; Suzenet, F.; Guillaumet, G. *Synlett* **2007**, 204−210. (e) Liebeskind, L. S.; Srogl, J. *Org. Lett.* **2002**, *4*, 979−981. (f) Kusturin, C. L.; Liebeskind, L. S.; Neumann, W. L. *Org. Lett.* **2002**, *4*, 983−985. (g) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 91−93. (h) Kusturin, C.; Liebeskind, L. S.; Rahman, H.; Sample, K.; Schweitzer, B.; Srogl, J.; Neumann, W. L. *Org. Lett.* **2003**, *5*, 4349−4352. (i) Alphonse, F. A.; Suzenet, F.; Keromnes, A.; Lebret, B.; Guillaumet, G. *Org. Lett.* **2003**, *5*, 803−805. (j) Oumouch, S.; Bourotte, M.; Schmitt, M.; Bourguignon, J.-J. *Synthesis* **2005**, 25−27.

(3) (a) Alphonse, F. A.; Suzenet, F.; Keromnes, A.; Lebret, B.; Guillaumet, G. *Synlett* **2002**, 447−450. (b) Aguilar-Aguilar, A.; Liebeskind, L. S.; Pena-Cabrera, E. *J. Org. Chem.* **2007**, *72*, 8539−8542.

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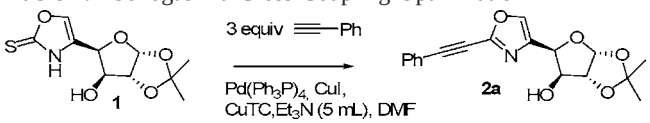
alternative tool in heteroaromatic C−C bond formations. The recent publication by Kappe of a modified desulfurative cross-coupling method, using direct reaction on thioamides under microwave assistance,[4] prompted us to disclose our own results.

The development of hybrid structures, involving small heterocyclic units connected on carbohydrate frames for the elaboration of nucleoside analogues and other biologically active molecules, is one of our main pipelines of research.[5] Targeting this goal, we have developed various methods to generate a large range of 1,3-oxazolidine-2-thiones (OZTs) and 1,3-oxazoline-2-thiones (OXTs) linked to carbohydrate skeletons.[6] Making use of the chemoselective S-alkylation, we have explored cyclocondensations and, for the first time, the Stille and Suzuki Pd cross-coupling reactions with alkylsulfanylated chiral heterocycles were accomplished.[7] With a view to shorten the process, Suzuki cross-coupling conditions on cyclic thionoamides, using microwave activation, have been tested successfully.[4] The Sonogashira coupling was the next protocol to be investigated because of its impressive impact on modern organic chemistry.[8] Extending the Sonogashira coupling to OXTs and OZTs would open new attractive synthetic routes to alkynyloxazoles and alkynyloxazolines—useful synthons in total synthesis and medicinal chemistry.[9]

When considering the Pd(0) coupling reactions with alkyl heteroarylsulfides or with thioamides, the major drawback in the processes is the relative amount of copper additives: Cu(I)-thiophene-2-carboxylate (CuTC), Cu(I)-3-methylsalicylate (CuMeSal), or CuBr·$Me_2S$ are always needed in more than one equivalent. Designing a new coupling process involving only catalytic amounts of copper cofactors would bring a major improvement in paving the way to extended uses of thiofunctionalized reaction partners for cross-coupling reactions. In the present letter, we report our first results on this new copper-catalyzed desulfurative protocol.

Our starting point for this investigation was to examine the coupling abilities of phenylacetylene with the D-xylofurano-derived OXT **1**, easily accessible from D-glucose.[6a] Our selected Sonogashira conditions required a Pd(0) source and CuI and $Et_3N$ in DMF in order to obtain an homogeneous medium; microwave heating was then applied, in accordance with previous works on Suzuki reactions.[2j,4] The different conditions explored are displayed in Table 1. Using the sole standard Sonogashira copper additive (CuI) in catalytic amount was ineffective (entry 1). Likewise (entry 2) replacing CuI by CuTC (effective copper additive for Suzuki coupling) did not result in a C−C coupling reaction. The implication of copper (I) in the reaction mechanism was taken into consideration on two distinct steps: (i) the transmetallation of copper iodide with the alkyne and (ii) the copper-assisted activation of the thiolactim-type intermediate. Consequently, we postulated that a conjunction of both copper (I) species in the medium would allow CuI and CuTC to react independently of one another, and this approach proved fruitful (Table 1).

**Table 1.** Sonogashira Cross-Coupling Optimization




| entry | $Et_3N$ (mL) | DMF (mL) | $Pd(Ph_3P)_4$ | CuI | CuTC | time (h) | yields[a] (%) |
|---|---|---|---|---|---|---|---|
| 1 | 5 | 2 | 0.1 | 0.5 | – | 1 | – |
| 2 | 5 | 2 | 0.1 | – | 2.2 | 1 | – |
| 3 | 5 | 2 | 0.1 | 0.5 | 2.2 | 1 | 63 |
| 4 | 5 | 2 | 0.1 | 0.5 | 1.1 | 1 | 85 |
| 5 | 5 | 2 | 0.05 | 0.5 | 1.1 | 1 | 83 |
| 6 | 5 | 2 | 0.05 | 0.5 | 0.5 | 1 | 85 |
| 7 | 5 | 2 | 0.05 | 0.5 | 0.1 | 1 | 79 |
| 8 | 5 | 2 | 0.05 | 0.5 | 0.1 | 1 | 73[a] |
| 9 | – | 2 | 0.05 | 0.5 | 0.1 | 1 | – |
| 10 | 5 | - | 0.05 | 0.5 | 0.1 | 1 | 33 |
| 11 | 5 | 2 | – | 0.5 | 0.1 | 1 | – |
| 12 | 5 | 2 | 0.05 | 0.5 | 0.1 | 0.25 | 77 |
| 13 | 5 | 2 | 0.05 | 0.1 | 0.1 | 0.25 | 56 |
| 14 | 5 | 2 | 0.05 | 0.1[b] | 0.1 | 0.25 | 33 |
| 15 | 5 | 2 | 0.05 | 0.5 | 0.1[c] | 0.25 | 53 |
| 16 | 5 | 2 | 0.05 | 0.5 | 0.1[d] | 0.25 | 75 |

[a] 1.5 equiv of phenylacetylene. [b] $Cu_2S$ was used instead of CuI. [c] CuBr·$Me_2S$ was used instead of CuTC. [d] CuMeSal was used instead of CuTC.

By mixing CuI and CuTC (entry 3), the 2-phenylethynyloxazole **2a** was obtained with a reasonable 63% yield. A search was then engaged for reducing the amount of copper additive. Decreasing the amount of CuTC to 1.1 equiv (entry 4) resulted in a dramatic improvement to 85% yield, and further reduction of the Pd(0) catalyst to 0.05 equiv (entry 5) did not lower the yield. Further, using CuTC in 0.5 equiv (entry 6) did not induce significative modification of the yield, whereas lowering CuTC down to 0.1 equiv (entry 7) only caused minor reduction of the yield to 79%.

Some additional modifications of the conditions were investigated: (i) Reducing phenylacetylene to 1.5 equiv (entry 8) still afforded the product **2** in fair yield. (ii) Removing one solvent resulted in no reaction without $Et_3N$ (entry 9), or to a low 33% yield in neat $Et_3N$ (entry 10). In this last case, the poor solubility of OXT 1 was involved.

(4) (a) Prokopcova, H.; Kappe, C. O. *J. Org. Chem.* **2007**, *72*, 4440−4448. (b) Prokopcova, H.; Kappe, C. O. *Adv. Synth. Catal.* **2007**, *349*, 448−452.

(5) (a) Yang, J.; Dowden, J.; Tatibouët, A.; Hatanaka, Y.; Holman. G. D. *Biochem. J.* **2002**, *367*, 533−539. (b) Girniene, J.; Tatibouët, Sackus, A. A.; Yang, J.; Holman, G. D.; Rollin, P. *Carbohydr. Res.* **2003**, *338*, 711−719.

(6) (a) Girniene, J.; Apremont, G.; Tatibouët, A.; Sackus, A.; Rollin, P. *Tetrahedron* **2004**, *60*, 2609−2619. (b) Tatibouët, A.; Lawrence, S.; Rollin, P.; Holman, G. D. *Synlett* **2004**, 1945−1948. (c) Leconte, N.; Silva, S.; Tatibouët, A.; Rauter, A. P.; Rollin, P. *Synlett* **2006**, 301−305.

(7) Leconte, N.; Pellegatti, L.; Tatibouët, A.; Suzenet, F.; Rollin, P.; Guillaumet G. *Synthesis* **2007**, 857−864.

(8) Chinchilla, R.; Najera, N. *Chem. Rev.* **2007**, *107*, 874−922.

(9) (a) Su, Q.; Dakin, L.A.; Panek, J. S. *J. Org. Chem.* **2007**, *72*, 2−24. (b) Wang, Y.; Janjic, J.; Kozmin, S. A. *Pure Appl. Chem.* **2005**, *77*, 1161−1169. (c) Cook, G. R. Manivannan, E.; Underdhal, T.; Lukacova, V.; Zhang, Y.; Balaz, S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4935−4939. (d) Paterson, I.; Tudge, M. *Tetrahedron* **2003**, *59*, 6833−6849. (e) Talley, J. J.; Bertenshaw, S. R.; Brown, D. L.; Carter, J. S.; Graneto, M. J.; Koboldt, C. M.; Masferrer, J. L.; Norman, B. H.; Rogier, D. J.; Zweifel, B. S.; Seibert, K. *Med. Res. Rev.* **1999**, *19*, 199−208.

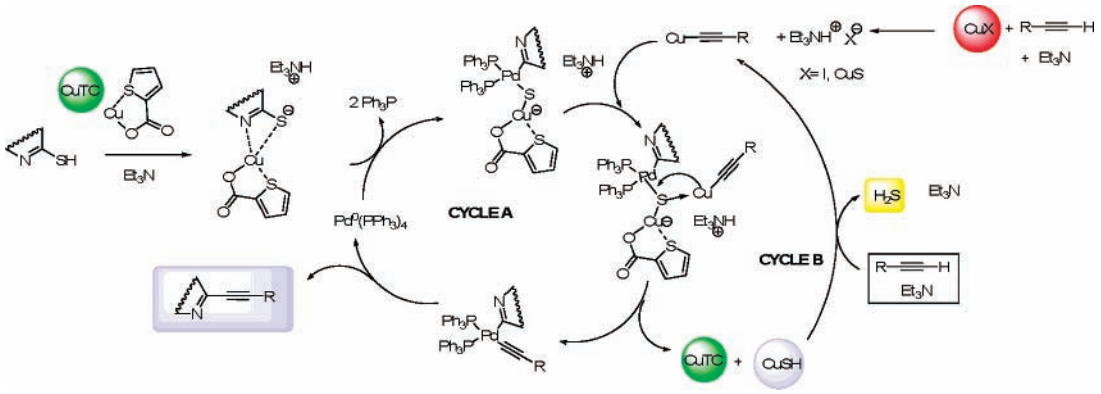


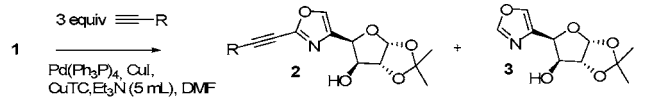

**Figure 1.** Proposed mechanism for the catalytic process.

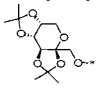
(iii) No reaction occurred after removing $Pd(Ph_3P)_4$ (entry 11). (iv) Reducing the reaction time to 15 min (entry 12) did not appreciably hamper the cross-coupling process (77% yield); the latter conditions were therefore adopted as a standard, using various OXTs and OZTs. (v) Bringing the catalytic quantity of CuI down to 10 mol % (entry 13) still kept the catalytic process efficient albeit resulting in a much lower yield.

This coupling reaction stands as a new alternative approach to the alkynyloxazole synthesis developed by Panek.[10] The most surprising aspect of this original copper-catalyzed desulfurative Sonogashira cross-coupling is the catalytic amounts of both palladium and CuTC used in the coupling process. From the first experiments performed, both copper (I) species were needed for the chemical coupling, which might mean that both copper complexes are implicated in the catalytic process (Figure 1). Based on the reaction scheme proposed by Kappe,[4] the copper (I) sulfide formed in situ might play a central role in the catalytic cycle. Indeed, by replacing CuI by $Cu_2S$ (entry 14), the catalytic reaction still proceeds, albeit with a poor 33% yield. Our proposed mechanism (Figure 1) highlights the important role of the alkynylcopper in the regeneration of CuTC and in the formation of CuSH which could then be a source of Cu(I) (cycle B) able to regenerate the alkynylcopper species. Under the same conditions, $CuBr{\cdot}Me_2S$ (entry 15) as well as CuMeSal (entry 16) could be used instead of CuTC, but a clear preference for the Suzuki Cu(I) additives had to be admitted.

One of our main streams of research is the structural-modulation potential of OXTs and OZTs connected to carbohydrate templates to mimick C-linked nucleosides. We have thus applied the selected conditions with different alkynes to react on OXT **1** (Table 2). A careful analysis of the reaction has shown the additional formation of the oxazole **3** in moderate proportions. The coupling reaction occurred with various alkynes in fair to good yields. Aromatic substitution on phenylacetylene (entries 2 and 3) induces an important yield variation, especially with the fluoro derivative **2c**, which undergoes coupling with a moderate yield and produces a significant amount of the reduced compound **3**; the reactivity of alkyne **3c** is clearly perturbed by the electron-withdrawing effect of fluorine.

**Table 2.** Variation of Alkynes




| entry | alkyne, R = | **2**, yields | **3**, yields |
|---|---|---|---|
| 1 | phenyl | **2a**, 77% | 7% |
| 2 | *p*-methoxyphenyl | **2b**, 63% | 11% |
| 3 | *p*-fluorophenyl | **2c**, 42% | 21% |
| 4 | *n*-pentyl | **2d**, 78% | 12% |
| 5 | methoxymethyl | **2e**, 66% | 23% |
| 6 | triethylsilyl | **2f**, 67% | 21% |
| 7 |  | **2g**, 58% | 24% |

Standard protocol : alkyne (3 equiv), CuI (0.5 equiv), CuTC (0.1 equiv), DMF (2 mL), $Et_3N$ (5 mL), MW 15 min.

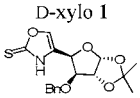
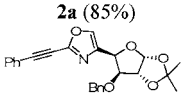
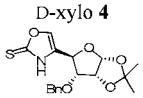
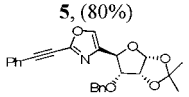
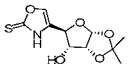
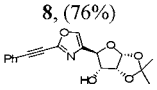
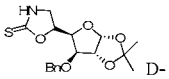
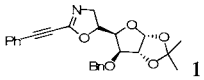
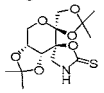
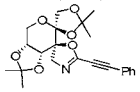
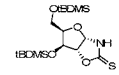
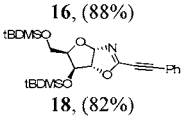
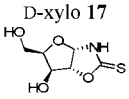
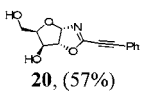
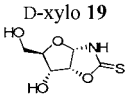
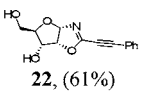
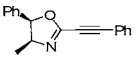
Heptyne proved as reactive as phenylacetylene (entry 4) with a good 78% yield of **2d**; however, slightly reduced efficiency was observed in the formation of **2e** and **2f** with enhanced production of oxazole (entries 5 and 6).[11] Finally, the process was also tested on a complex carbohydrate-derived alkyne, 1-*O*-propargyl-2,3;4,5-di-*O*-isopropylidene-*β*-D-fructopyranose (entry 7), with which a reasonable 58% coupling yield could be obtained. In all cases, the oxazole formation (7−24% yield) was indicative of a competing reaction during the transmetallation process.

The scope of the reaction was then explored in two different directions (Table 3); one consisted in changing the carbohydrate platform bearing the OXT heterocycle (entries

(10) Langille, N. F.; Dakin, L. A.; Panek, J. S. *Org. Lett.* **2002**, *4*, 2485−2488.

(11) The interesting triethylsilylacetylene gave a good yield of the coupling product, while the trimethylsilyl analogue showed important instability during the process and no coupling product could be detected.

**Table 3.** Substrate and Heterocycle Modulation

| entry | starting material | product (yield) | oxazole (yield) |
|---|---|---|---|
| 1 | D-xylo **1** | **2a** (85%) | **3** (7%) |
| 2 |  D-xylo **4** |  **5**, (80%) | **6**, (5%) |
| 3 |  D-ribo **7** |  **8**, (76%) | **9**, (8%) |
| 4 |  D-ribo **10** |  **11**, (73%) | **12**, (6%) |
| 5 |  D-gluco **13** |  **4**, (83%) | -[a] |
| 6 |  D-fructo **15** |  **16**, (88%) | -[a] |
| 7 |  D-xylo **17** |  **18**, (82%) | -[a] |
| 8 |  D-xylo **19** |  **20**, (57%) | -[a] |
| 9 |  D-ribo **21** |  **22**, (61%) | -[a] |
| 10 |  **23** |  **24**, (62%) | -[a] |

[a] Not detected.

1−4), and the other focused on the parent OZTs connected with miscellaneous templates (entries 5−10). An overview of the reactions demonstrated the ability of the method for C−C bond formation on either aromatic OXTs or chiral OZTs. Coupling phenylacetylene with the α-D-xylo derivatives **1** and **4** and α-D-ribo derivatives **7** and **10** unvaryingly afforded good yields (73−85%) of hybrid alkynes **2a**, **5**, **8**, and **11**, respectively. In all the above cases, the reductive process gave small (5−8%) yields of oxazoles **3**, **6**, **9**, and **12**, whereas no competing reduction could be detected in the case of OZT derivatives.

The first carbohydrate-linked OZT **13** to be tested was closely related to OXT **4**, and the phenylacetylene cross-coupling proved as efficient as on the aromatic OXT. A spiro-OZT connected to a 1,2;4,5-di-*O*-isopropylidene-D-fructopyrano frame (**15**) was then selected because of the known stereoinductive ability of this carbohydrate template; an excellent 88% yield of alkyne **16** was obtained.[12] We then moved to pentose derivatives **17**, **19**, and **21**, in which the OZT is anchored on the anomeric position. A good coupling efficiency was observed with the *O*-silyl-protected D-xylo OZT **17**, with an 82% yield of the resulting alkynyl oxazoline **18**. A drop of reactivity was noted in the case of unprotected OZTs **19** and **21**, with D-xylo- and D-ribo-oxazolines **20** and **22** being produced in 57% and 61% yield, respectively. Nevertheless, the above experiments clearly indicate that unprotected hydroxyls are compatible with our coupling process; such complex alkynyl derivatives could therefore be produced in only two steps from the corresponding pentoses.[5b] The last example (entry 10) involved a non-carbohydrate norephedrine-derived molecule **23**,[13] which was shown to behave similarly by delivering a 62% yield of the substituted 1,3-oxazoline **24**. An overall analysis of the various experiments performed demonstrates the versatility of our cross-coupling protocol, in which diverse sensitive carbohydrate derivatives, either O-protected with benzyl/silyl ethers or acetal groups, or even unprotected ones, can be used under microwave heating conditions at 100 °C.

In summary, this exploration of a novel Sonogashira cross-coupling has given us the opportunity not only to disclose the first alkynyl C−C bond formation using thionocarbamates but moreover to disclose the possibility to use copper(I) in catalytic amount and to suggest, consequently, a mechanism (Figure 1) in which CuSH might play the central role. Further exploration of this mechanism to extend the catalytic copper-(I) potential will be disclosed in due time.

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**Supporting Information Available:** Analytical data and spectra ($^1$H and $^{13}$C NMR) for all new products; typical procedure for the palladium-catalyzed Sonogashira reaction. This material is available free of charge via the Internet at http://pubs.ac.org.

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